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(54) Title: COMBINATION THERAPY FOR HIV INFECTION

(57) Abstract

The combination of the HIV protease inhibitor Compound J and one or more of nevarapine or an α-APA derivative is useful in theinhibition of HIV protease, the inhibition of HIV reverse transcriptase, the prevention or treatment of infection by HIV and the treatment of AIDS, either as compounds, pharmaceutically acceptable salts, pharmaceutical composition ingredients, whether or not in combination with other antivirals, immunomodulators, antibiotics or vaccines. Methods of treating AIDS and methods of preventing or treating infection by HIV are also described.

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TITLE OF THE INVENTION

COMBINATION THERAPY FOR HIV INFECTION

FIELD OF THE INVENTION

The combination in this invention is useful in the inhibition of HIV protease, the inhibition of HIV reverse transcriptase, the treatment of infection by HIV and in the treatment of AIDS and/or ARC (i.e., AIDS related complex), either as compounds, pharmaceutically acceptable salts or esters (when appropriate), pharmaceutical composition ingredients, whether or not in combination with other antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. Methods of treating AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV are also disclosed.

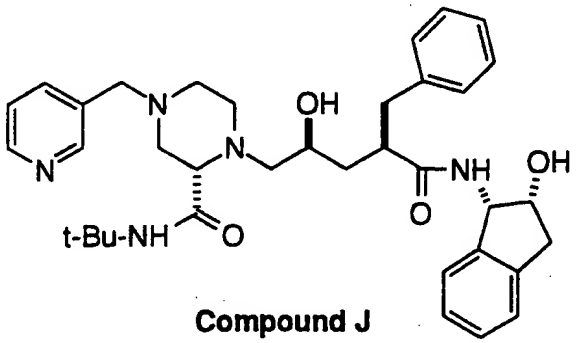
BACKGROUND OF THE INVENTION

A retrovirus designated human immunodeficiency virus (HIV) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV. A common feature of retrovirus replication is the extensive post-translational processing of precursor polyproteins by a virally encoded protease to generate mature viral proteins required for virus assembly and function. Inhibition of this processing prevents the production of normally infectious virus. For example, Kohl, N.E. et al., *Proc. Nat'l Acad. Sci.*, *85*, 4686 (1988), demonstrated that genetic inactivation of the HIV encoded protease resulted in the production of immature, non-infectious virus particles. These results indicate that inhibition of the HIV protease represents a viable method for the treatment of AIDS and the prevention or treatment of infection by HIV.

Nucleotide sequencing of HIV shows the presence of a pol gene in one open reading frame [Ratner, L. et al., *Nature* , *313*, 277 (1985)]. Amino acid sequence homology provides evidence that the pol

sequence encodes reverse transcriptase, an endonuclease and an HIV protease [Toh, H. et al., *EMBO J.*, *4*, 1267 (1985); Power, M.D. et al., *Science*, *231*, 1567 (1986); Pearl, L.H. et al., *Nature*, *329*, 351 (1987)].

The compound disclosed and referred to as "Compound J" in EPO 541,168, which published on May 12, 1993, is a potent inhibitor of HIV protease and is useful in the prevention of infection by HIV, the treatment of infection by HIV and the treatment of AIDS or ARC, without significant side effects or toxicity.



Compound J

One substantial and persistent problem in the treatment of AIDS has been the ability of the HIV virus to develop resistance to the individual therapeutic agents employed to treat the disease. To solve this problem, a combination therapy for AIDS has been discovered by applicants.

Applicants demonstrate that the combination of compounds of this invention is an effective inhibitor of HIV protease.

In the present invention, applicants co-administer a potent HIV protease inhibitor, such as Compound J, or other chemical entities, with a non-nucleoside HIV reverse transcriptase inhibitor such as nevarapine or an α-anilinophenylacetamide (i.e., α-APA) derivative. Optionally, a third component which is a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, ddI or ddC, is added to the combination. This combination therapy is a method to enhance the

effectiveness in treating AIDS and to preclude the development of resistance to the individual therapeutic agents.

SUMMARY OF THE INVENTION

The instant invention involves a combination of compounds, which is Compound J and a non-nucleoside HIV reverse transcriptase inhibitor selected from nevarapine or an α-APA derivative, and, optionally, a nucleoside inhibitor of HIV reverse transcriptase selected from AZT, ddI or ddC, or a pharmaceutically acceptable salt or ester thereof.

In one embodiment of the invention is the combination which is Compound J and nevarapine.

In a class is the combination which is Compound J and an α-APA derivative.

In a subclass is the combination wherein the α-APA derivative is R89439.

In a second subclass is the combination wherein the α-APA derivative is R18893.

Illustrative of the invention is the combination which is Compound J, nevarapine and the nucleoside inhibitor of HIV reverse transcriptase.

Further illustrating the invention is the combination wherein the the nucleoside inhibitor of HIV reverse transcriptase is AZT.

Exemplifying the invention is a method of inhibiting HIV protease, comprising administering to a suitable mammal in need of such treatment an effective amount of the combination.

An example of the invention is a method of inhibiting HIV reverse transcriptase, comprising administering to a suitable mammal in need of such treatment an effective amount of the combination.

An illustration of the invention is a method of preventing infection of HIV, or of treating infection by HIV, or of treating AIDS

or ARC, comprising administering to a suitable mammal in need of such treatment an effective amount of the combination.

More specifically illustrating the invention is a pharmaceutical composition useful for inhibiting HIV protease, comprising an effective amount of the combination, and a pharmaceutically acceptable carrier.

Specifically exemplifying the invention is a pharmaceutical composition useful for inhibiting HIV reverse transcriptase, comprising an effective amount of the combination, and a pharmaceutically acceptable carrier.

A further example is a pharmaceutical composition useful for preventing or treating infection of HIV, or for treating AIDS or ARC, comprising an effective amount of the combination and a pharmaceutically acceptable carrier.

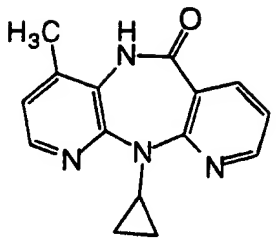
DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

This invention is concerned with the combination of certain compounds, or pharmaceutically acceptable salts thereof, in the inhibition of HIV protease, the inhibition of HIV reverse transcriptase, the prevention or treatment of infection by HIV and in the treatment of the resulting acquired immune deficiency syndrome (AIDS). The combination is defined as follows:

Compound J and a non-nucleoside inhibitor of HIV reverse transcriptase selected from nevarapine and an α-APA derivative, or pharmaceutically acceptable salts thereof.

The HIV protease inhibitor Compound J is synthesized by the protocol of EP 0 541 168, published 12 May 1993. Compound J is N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butyl-carboxamido)-piperazinyl))-pentaneamide, or pharmaceutically acceptable salt thereof.

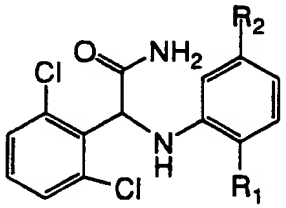
Nevarapine is 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-*e*][1,4]diazepin-6-one,



Nevarapine

Nevarapine is synthesized by the procedure described in Hargrave, K.D. et al., *J. Med. Chem.*, *34*, 2231-2241 (1991) and Klunder, K.D. et al., *J. Med. Chem.*, *35*, 1887-1897 (1992).

α-APA derivatives are α-anilinophenylacetamide derivatives of the formula:



α-APA derivative

wherein R_1 is methoxy, nitro or C(O)-CH_3 and R_2 is hydrogen or methyl. Of particular interest in the instant combination are the α-APA derivatives R89439 and R18893. R89439 is the α-APA derivative wherein R_1 is C(O)-CH_3 and R_2 is methyl. R18893 is the α-APA derivative wherein R_1 is nitro and R_2 is hydrogen. α-APA derivatives are made by the procedure described in PCT patent application, International Publication No. WO92/00952, published 23 January 1992.

The pharmaceutically acceptable salts of the present invention (in the form of water- or oil-soluble or dispersible products) include the conventional non-toxic salts or the quaternary ammonium salts which are formed, e.g., from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate,

camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others. Other pharmaceutically acceptable salts include the sulfate salt ethanolate and sulfate salts.

The pharmaceutically acceptable salts of the combination of the instant invention include the combination wherein one of the individual components is in the form of a pharmaceutically acceptable salt, or the combination wherein all of the individual components are in the form of pharmaceutically acceptable salts, or a pharmaceutically acceptable salt of the combined components (i.e., a salt of the combination). In one embodiment of the present invention, the sulfate salt of the combination is utilized.

The pharmaceutically acceptable esters in the present invention refer to non-toxic esters, preferably the alkyl esters such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl or pentyl esters, of which the methyl ester is preferred. However, other esters such as phenyl-C_{1-5} alkyl may be employed if desired.

Esterification of alcohols, such as Compound J of the present invention, is performed by a variety of conventional procedures, including reacting the alcohol group with the appropriate anhydride, carboxylic acid or acid chloride. These reactions, as well as other methods of esterification of alcohols, are readily apparent to the skilled artisan.

Reaction of the alcohol with the appropriate anhydride is carried out in the presence of an acylation catalyst, such as 4-DMAP (4-dimethylaminopyridine, also known as N,N-dimethylaminopyridine), pyridine, or 1,8-bis[dimethylamino]napthalene.

Reaction of the alcohol with the appropriate carboxylic acid is carried out in the presence of a dehydrating agent and, optionally, an acylation catalyst. The dehydrating agent, which serves to drive the reaction by the removal of water is selected from dicyclohexylcarbodiimide (DCC), 1-[3-dimethylaminopropyl]-3-ethylcarbodiimide (EDC) or other water soluble dehydrating agents.

Alternatively, reaction of the alcohol with appropriate carboxylic acid can also result in esterification, if performed instead in the presence of trifluoroacetic anhydride, and, optionally, pyridine. A further variant is reacting the alcohol with appropriate carboxylic acid in the presence of N,N-carbonyldiimidazole with pyridine.

Reaction of the alcohol with the acid chloride is carried out with an acylation catalyst, such as 4-DMAP or pyridine.

Selective esterification of Compound J is performed by a variety of methods known to the skilled artisan. In one method, the alcohol is first esterified with a trichloroethyl derivative (e.g., mono-trichloroethyl succinate). After chromatographic isolation of the preferred ester, reductive elimination of the tricholoroethyl group is carried out by reaction with zinc dust in acetic acid. Alternatively, another method of selective esterification is the hydrolysis of the bis-ester.

The combination of compounds of the present invention is useful in the inhibition of HIV protease, the inhibition of HIV reverse

transcriptase, the prevention or treatment of infection by human immunodeficiency virus (HIV) and the treatment of consequent pathological conditions such as AIDS. Treating AIDS or preventing or treating infection by HIV is defined as including, but not limited to, treating a wide range of states of HIV infection: AIDS, ARC, both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by e.g., blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

For these purposes, the combinations of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles.

Thus, in accordance with the present invention there is further provided a method of treating and a pharmaceutical composition for treating HIV infection and AIDS. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically effective amount of each compound in the combination of the present invention.

These pharmaceutical compositions may be in the form of orally-administrable suspensions or tablets; nasal sprays; sterile injectable preparations, for example, as sterile injectable aqueous or oleaginous suspensions or suppositories.

In accordance with the method of the present invention, the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. For example, in a two-component combination which is the HIV protease inhibitor, Compound J, and the non-nucleoside HIV reverse transcriptase

inhibitor, nevarapine, treatment with nevarapine can commence prior to, subsequent to or concurrent with commencement of treatment with Compound J. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

When administered orally as a suspension, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

When administered by nasal aerosol or inhalation, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

When rectally administered in the form of suppositories, these compositions may be prepared by mixing the drug with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquidify and/or dissolve in the rectal cavity to release the drug.

The compounds of this invention can be administered to humans in the dosage ranges specific for each compound. Compound J, or a pharmaceutically acceptable salt thereof, is administered orally in a dosage range between about 40 mg and about 4000 mg per day, divided into between one and four doses per day. Nevarapine, or a pharmaceutically acceptable salt thereof, is administered orally at a dosage range between about 12 mg per day and about 500 mg per day, given in a single dose per day. The α-APA derivatives, and in particular, R89439 and R18893, or pharmaceutically acceptable salts thereof, are administered orally at a dosage range between about 100 mg per day and about 1000 mg per day, divided into between one and 3 doses per day. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

The combination of the present invention can also be combined with an optional third antiviral component which is a nucleoside inhibitor of HIV reverse transcriptase. For example, the combination of this invention may be effectively administered, whether at periods of pre-exposure and/or past exposure, in combination with effective amounts of the AIDS antivirals AZT, ddI or ddC, known to those of ordinary skill in the art.

TABLE 1
Antivirals

Drug Name	Manufacturer	Indication
ddI Dideoxyinosine	Bristol-Myers (New York, NY)	AIDS, ARC
ddC Dideoxycytidine	Hoffman-LaRoche (Nutley, NJ)	AIDS, ARC
Zidovudine, AZT	Burroughs-Wellcome (Research Triangle Park)	AIDS, adv, ARC, pediatric AIDS, Kaposi's sarcoma, asymptomatic HIV infection, less severe HIV disease, neurological involvement, in combination with other therapies

AZT is synthesized by the methods of J.P. Horwitz et al., *J. Org. Chem.*, *29*, 2076 (1964); R.P. Glinski et al., *J. Org. Chem.*, *38*, 4299 (1973); and C.K. Chu et al., *Tetrahedron Letters*, *29*, 5349 (1988). Application of AZT as a therapeutic drug in the treatment of AIDS is disclosed in U.S. Patent No. 4,724,232.

The compound ddC is synthesized by the methods of J.P. Horwitz et al., *J. Org. Chem.*, *32*, 817 (1967); R. Marumoto and M. Honjo, *Chem. Pharm. Bull.*, *22*, 128 (1974); and T-S. Lin et al., *J. Med. Chem.*, *30*, 440 (1987). Application of ddC as a therapeutic drug in the treatment of AIDS is disclosed in U.S. Patent Nos. 4,879,277 and 5,028,595.

The compound ddI is synthesized by the methods of U.S. Patent No. 5,011,774; and V. Bhat et al., *Synthetic Commun.*, 22(10), 1481-86 (1992). Application of ddI as a therapeutic drug in the treatment of AIDS is disclosed in U.S. Patent No. 5,254,539.

Preferred combinations are simultaneous or alternating treatments of an inhibitor of HIV protease and a non-nucleoside inhibitor of HIV reverse transcriptase. An optional third component in the instant combination is a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, ddC or ddI. These combinations may have synergistic effects on limiting the spread of HIV. Thus, the present invention includes combinations of the HIV protease inhibitor Compound J, with a non-nucleoside HIV reverse transciptase inhibitor selected from nevarapine or α-APA and a nucleoside HIV reverse transcriptase inhibitor selected from AZT, ddI or ddC.

EXAMPLE 1

Protocol for pharmacokinetic evaluation of combination therapy with only nevarapine

This is a fixed-sequence, randomized, two-period, parallel protocol to measure the effect of nevarapine on the pharmacokinetics and safety and tolerability of Compound J, an HIV-1 protease inhibitor in seronegative patients. The pharmacokinetics and safety of a single 600 mg oral dose of Compound J is measured at baseline (Period I) and again (Period II) following administration of nevarapine at 400 mg once a day (or a placebo instead of nevarapine) for six days. The study design is outlined in detail in the Table. Plasma concentration of Compound J is determined at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours following the dose. Laboratory safety is measured at predose and 12 hours after Compound J on Day 1.

Total plasma clearance of Compound J is calculated as the dose divided by the total area under the plasma concentration-time curve from zero to infinity. The apparent half-life is estimated from

the slope of the terminal phase fitted to the log plasma concentration-time curve by the method of least squares. The concentration of Compound J in plasma or plasma filtrate is determined by analysis on HPLC, monitored for absorbance at 220 nm.

TABLE 2

Period I (day O)	
Period I (day 1)- Compound J pharmacokinetics	Compound J single 600 mg dose plasma profile (12 h)
Period I-to-II- interim treatment (days 2-7)	nevarapine 400 mg once each day

EXAMPLE 2

Protocol for combination therapy with only nevarapine

In this protocol to show the antiviral activity of one regimen of Compound J given with nevarapine in HIV-seronegative subjects, Compound J is administered at a dose of 600 mg four times a day and nevarapine is administered at 400 mg once a day. Antiviral activity is measured before and during combination therapy by measuring serum levels of the HIV p24 antigen, serum levels of HIV RNA, and CD4 lymphocyte counts.

EXAMPLE 3

Protocol for pharmocokinetic evaluation of combination therapy with only α-APA

This is a protocol to show effects of an α-APA derivative on plasma concentration profile of Compound J in HIV-seronegative subjects. It is a fixed-sequence, randomized, two-period, parallel protocol. The pharmacokinetics and safety of a single 600 mg oral dose of Compound J is measured at baseline (Period I) and again (Period II) following administration of the α-APA derivative at doses ranging from 25 mg up to 500 mg from between one and three times a day (or a placebo instead of the α-APA derivative) for six days.

EXAMPLE 4

Protocol for combination therapy with only α-APA

In this protocol to show the antiviral activity of one regimen of Compound J given with an α-APA derivative in HIV-seronegative subjects, Compound J is administered at a dose of 600 mg four times a day and the α-APA derivative is administered at doses ranging from 25 mg up to 500 mg from between one and three times a day. Antiviral activity is measured before and during combination therapy by measuring serum levels of the HIV p24 antigen, serum levels of HIV RNA, and CD4 lymphocyte counts.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptions, or modifications, as come within the scope of the following claims and its equivalents.

WHAT IS CLAIMED IS:

1. A combination of compounds, which is Compound J and a non-nucleoside HIV reverse transcriptase inhibitor selected from nevarapine or an α-APA derivative, and, optionally, a nucleoside inhibitor of HIV reverse transcriptase selected from AZT, ddI or ddC, or a pharmaceutically acceptable salt or ester thereof.

2. The combination of Claim 1, which is Compound J and nevarapine.

3. The combination of Claim 1, which is Compound J and an α-APA derivative.

4. The combination of Claim 3, wherein the α-APA derivative is R89439.

5. The combination of Claim 3, wherein the α-APA derivative is R18893.

6. The combination of Claim 1, which is Compound J, nevarapine and the nucleoside inhibitor of HIV reverse transcriptase.

7. The combination of Claim 6, wherein the nucleoside inhibitor of HIV reverse transcriptase is AZT.

8. A method of inhibiting HIV protease, comprising administering to a suitable mammal in need of such treatment an effective amount of the combination of Claim 1.

9. A method of inhibiting HIV reverse transcriptase, comprising administering to a suitable mammal in need of such treatment an effective amount of the combination of Claim 1.

10. A method of preventing infection of HIV, or of treating infection by HIV, or of treating AIDS or ARC, comprising administering to a suitable mammal in need of such treatment an effective amount of the combination of Claim 1.

11. A pharmaceutical composition useful for inhibiting HIV protease, comprising an effective amount of the combination of Claim 1, and a pharmaceutically acceptable carrier.

12. A pharmaceutical composition useful for inhibiting HIV reverse transcriptase, comprising an effective amount of the combination of Claim 1, and a pharmaceutically acceptable carrier.

13. A pharmaceutical composition useful for preventing or treating infection of HIV, or for treating AIDS or ARC, comprising an effective amount of the combination of Claim 1, and a pharmaceutically acceptable carrier.